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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/243,102	02/02/1999	IAN MACLACHLAN	16303-73-2	2007

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/243,102	MACLACHLAN ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14-35,37-41 and 43-61* is/are pending in the application.

4a) Of the above claim(s) *29-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,14-28,35,37-41 and 43-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Detailed Action

This Office action is in response to the communications filed 4-19-04.

Claims 1-12, 14-35, 37-41, 43-61 are pending in the instant application.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

The declaration filed on 4-19-04 under 37 CFR 1.131 is sufficient to overcome the 102 reference.

Applicant's arguments, filed 4-19-04, with respect to the rejection(s)of claim(s) 1-12, 14-28, 35, 37-41, 43-61 under 102 and 103 have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made as indicated in the 103 below.

New Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-12, 14-28, 35, 37-41, 43-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wheeler et al in view of Hung et al, the combination in view of Fulton et al, Zhuang et al and Chaudhary et al.

The claims are drawn to methods of treating a tumor in a mammal comprising the distal administration of a serum stable (nuclease resistant) nucleic acid-lipid particle comprising a fully encapsulated nucleic acid comprising an expressible gene encoding HSVTK (a suicide enzyme) or IL-12 (a cytokine), and optionally further comprising administration of a chemotherapeutic agent or prodrug either before or after administration of the nucleic acid-lipid particle, or wherein the expressible gene encodes a suicide enzyme, apoptin (a tumor suppressor protein) or *Pseudomonas* exotoxin, and which particles comprise a cationic lipid (e.g. having a pKa from about 4 to 11), neutral lipid and lipid conjugate that prevents aggregation during formulation, and which tumor is a colorectal, sarcoma or melanoma tumor, and which lipid conjugate exchanges out of an outer lipid monolayer at a rate faster than that of PEG-CerC20, and which particle is substantially devoid of detergents and organic solvents, and which particle has a nucleic acid to lipid ratio greater than at least 25 mg nucleic acid to a mmole of lipid.

Wheeler et al (USPN 6,586,410) teach methods of making and systemically (IV, IP) administering (col. 26, line 34-col. 28, line 33; claims 26 and 28) lipid nucleic acid particles of uniform size and between 50 and 200 nm (claim 3) stable to nuclease degradation (col. 38, line 9-52; col. 48, line 54-col. 49, line 18) comprising a cationic lipid with a pKa between 4 and 11 (DODAC or DOPE) a neutral lipid (col. 10, line 47-col. 11, line 46) and a PEG-lipid conjugate that prevents aggregation (col. 13, lines 40-65; figure 46; claim 1, 7-11), at a ratio of at least 25 mg nucleic acid to mmole of lipid (claims 14-16) is substantially devoid of detergent (col. 35, line 14-col. 37, line 40), and which nucleic acid is encapsulated within the lipids and encodes a therapeutic protein (col. 29, line 11-col. 30, line 23).

Hung et al (USPN 6,683,059) teach methods of treating various tumors in a mammal (col. 43, line 17-col. 44, line 28; 44, line 35-col. 45, line 53) comprising the systemic administration (IV or IP) (col. 30, line 63-col. 31, line 8; col. 39, line 36-col. 40, line 5; col.46, line 62-col. 47, line 11) of nucleic acid-lipid particles or complexes, including nucleic acids encapsulated in lipid particles (col. 24, line 29- col. 26, line 63), which nucleic acids encode therapeutic polynucleotides (ribozymes) or polypeptides, and optionally further comprising the administration of a chemotherapeutic agent either before or after administration of the nucleic acid-lipids (col. 42, lines 1-25; col. 25-26; examples VI and VII, col. 45-50, esp. col. 47, lines 1-11).

The primary references of Wheeler and Hung do not teach treating melanoma, sarcoma or colorectal tumors, nor the administration of nucleic acids encoding IL-12, HSVTK, apoptin or exotoxin.

Fulton et al (USPN 6,508,550) teach methods of treating melanoma, sarcoma and colorectal tumors comprising the administration of nucleic acids encoding a tumor suppressor protein, interleukin 12 (IL-12) or thymidine kinase (HSVTK), optionally in combination with a prodrug administered either before or after administration of lipids and nucleic acids encoding either the tumor suppressor protein, IL-12 or HSVTK (abstract; col. 2; col. 10, line 53-col. 11, line 7; col. 33; col. 52-53; col. 56-58; col. 60; col. 62-63).

Zhuang et al (Cancer Res. 55: 486-489) teach the administration of apoptin to sarcoma cells to induce apoptosis (abstract and figure 4 on page 488).

Chaudhary et al (Nature 339: 394-397) teach the lysis of target cells by Pseudomonas exotoxin (abstract, figure 3 and table 1 on page 396).

It would have been obvious to one of ordinary skill in the art to make lipid nucleic acid particles claimed in the instant application using the methods previously described by Wheeler, which also teaches methods of encapsulating nucleic acids that encode therapeutic proteins, and delivering them to target cells in an organism because Wheeler teach methods of making the particles claimed and encapsulating nucleic acids into these lipid nucleic acid particles, as well as teaching delivery and expression of recombinant proteins in target cells in vivo following systemic administration. It would have been obvious to deliver the therapeutic nucleic acids by systemic administration to tumors for tumor treatment because Hung teaches the administration of nucleic acids encoding therapeutic proteins and polypeptides using lipid nucleic acid particles, as well as teaching treatment of various tumors following nucleic acid delivery and expression. One would have expected that the methods of making the particles and delivering encapsulated nucleic acids described by Wheeler would provide for the therapeutic effects of recombinantly

expressed therapeutic polypeptides because adequate delivery of nucleic acids to target cells was previously taught by Wheeler and tumor treatment following delivery and expression of therapeutic polypeptides was previously taught by Hung. One of ordinary skill in the art would have been motivated to deliver nucleic acids encoding IL-12 because this cytokine provides an immune response that enhances tumor cell kill, as taught previously by Fulton. One would have been motivated to deliver nucleic acids encoding either HSVTK, apoptin or exotoxin to tumor or other cancer cells including sarcoma, melanoma and colorectal cells because these molecules are known to enhance target cell killing following their delivery and expression as taught previously by Fulton, Zhuang and Chaudhary. It would have been obvious to one of ordinary skill in the art to treat sarcoma, melanoma or colorectal tumors with nucleic acids encapsulated in lipid particles, which nucleic acids encode a tumor suppressor protein, IL-12, HSVTK, apoptin or *Pseudomonas* exotoxin because these therapeutic molecules have been taught and utilized previously by Fulton, Hung, Zhuang and Chaudhary to treat tumors or cancer cells and one of ordinary skill in the art would have expected that the encapsulated nucleic acids (using the methods taught by Wheeler) are delivered to the target cancer cell or tumor site following distal administration and in therapeutically effective concentrations, inhibiting tumor cell growth and/or viability, thereby providing tumor treatment. One of ordinary skill in the art would have been motivated to administer the therapeutic, encapsulated nucleic acids to tumor cells optionally in combination with chemotherapeutic agents or prodrugs because Fulton and Hung have taught the enhanced treatment of target tumor cells using these combined therapies, and one of ordinary skill in the art would have expected that enhanced tumor cell kill or tumor treatment is obtained following administration of the nucleic acid-lipid particles as taught previously by Wheeler,

either preceding or following prodrug or chemotherapeutic agent administration. One of ordinary skill in the art would have been motivated to encapsulate these therapeutic nucleic acids in lipid particles because Wheeler taught previously that enhanced protection of the nucleic acids from nuclease degradation is obtained upon lipid encapsulation of the nucleic acids. And one of ordinary skill in the art would have expected that enhanced tumor treatment is obtained using encapsulated nucleic acids because Wheeler and Hung have shown that encapsulation or lipid mediated delivery lead to enhanced nucleic acid stability, which in turn leads to enhanced nucleic acid delivery to the tumor sites, thereby providing delivery of appropriate therapeutic concentrations of the nucleic acids at a tumor site.

Therefore, the claimed invention would have been obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ
6-22-04

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